REMARKS

Claims 1, 4, 7-9 are now pending in the application. Claim 9 has been withdrawn from consideration by the Examiner as being directed to a non-elected invention. Claims 1 and 4 are currently amended. No claims are cancelled or newly added by this amendment. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

EXAMINER INTERVIEW

On June 4, 2009, Applicants' representative, Fernando Alberdi, and Examiner Borin conducted a telephonic interview discussing the rejections under § 112, second paragraph, and the § 101 non-statutory rejection. No substantive agreement was reached but Applicants agreed to provide the Examiner with further explanation in these remarks. See Overview of Applicants' Method below.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 4, 7 and 8 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicants regard as the invention. These rejections are respectfully traversed.

Overview of Applicants' Method

When studying the properties of complex molecules in virtual space using a conventional 3D analysis, such as the 3D QASR analysis, a considerable load is placed on the resources of the computer that performs the analysis and graphical rendering. This load can lead to problems where the computed images are rendered too slowly on standard personal computers. Applicants' computer-based method is designed to be very efficient and can thus allow sophisticated 3D analysis techniques to be utilized by researchers who do not have access to expensive, high-powered analysis workstations.

The applicants' computer-based method achieves its efficiency through a clever use of data reduction steps that replace large complex data sets with smaller, more rapidly computed data sets, all without discarding important analytical details. By way of overview, the applicants' method may be summarized as follows. In the summary below, reference is made using paragraph numbers [in brackets] which correspond to the numbered paragraphs of the published application 2006/008007:

1. Begin with a set of plural molecules to be analyzed [0115].

2. Place the molecules into virtual space where the individual atoms are represented by points at given xyz coordinates [0116] – this is the atomic coordinate model 4 [0116].

3. Calculate distances among pairs of virtual atoms, and when two virtual atoms are close to each other, replace the pair with a generated point, called a pseudo-atom in virtual space [0116].

4. Assign to each generated point a weight corresponding to the number of atoms it replaces [0116]. Note that this step results in significant data reduction, which reduces the computational load on the computer.

Note that the applicants' method does not pay attention to the atom types (chemical elements) but only atomic positions of the molecules according to the represented point generation process. Thus, different chemical entities could be calculated in the same category.

The Examiner had questioned how the electrostatic and hydrophobic interactions between these representative points would be determined; on the assumption that these properties would differ between, for example, a carbon atom and a nitrogen atom. The answer is that the applicants' method does not care about which atom type is being substituted. Thus, nominal steric and hydrophobic values can be assigned to the represented point (e.g., charge = +1 and radius = 1 Angstrom). In the case of rapid molecular superposition evaluation function 2-A and indicator variables 2-D, interactions between the represented point and the atoms on the molecules may simply be calculated by the distance and the chemical entities of the atoms on the molecules.

5. In some cases, an entire functional group of atoms can be replaced by a single point [0117]. This replacement further reduces the data.

6. Continue performing the above data reduction steps until all virtual atoms/pseudo-atom points that are within a predefined close proximity have been combined. This results in an atomic coordinate model 7 [0119]. Note that this atomic

coordinate model represents a significant data reduction; it potentially represents many of the plural molecules with which we started.

7. Having constructed the atomic coordinate model, the next steps perform further data enhancement using a 3D quantitative structure-activity relationship (3D QSAR) technique. The classic 3D QSAR technique uses a probe atom located at a point in xyz space, and then calculates the steric and/or electrostatic interaction between the probe atom and the molecule being studied. In this case, the individual atoms of the starting set of plural molecules are each used as a probe atom in assessing the steric and/or electrostatic interaction with the atomic coordinate model [0120].

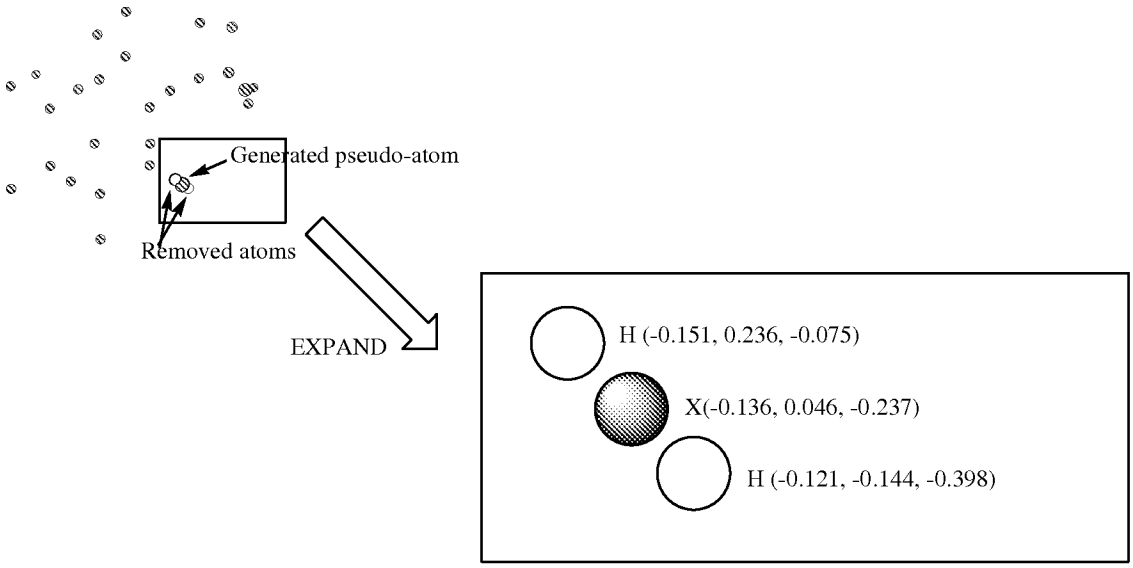
The above 3D QSAR step thus associates molecular interactivity information with each virtual atom / pseudo-atom of the atomic coordinate model. Thus, the atomic coordinate model has not only xyz information but also interactivity information.

8. Next, a further data reduction step is performed. This data reduction step takes advantage of the fact that the atomic coordinate model now has interactivity information. Specifically, a statistical partial least square (PLS) operation is performed to generate a set of principal "components." The PLS operation can significantly reduce the size of the data set by reducing the potentially hundreds or thousands of points in the atomic coordinate model with a set of principal components which are "orthogonal" to one another. These components are each associated with an object variable, such as activity value [0121].

9. Having thus represented the atomic coordinate models (xyz) in principal component space, a desired bilological activity (or other such object variable) can be

focused on, and the atomic coordinate model that best fits that desired activity can be quickly identified and displayed in 3D space.

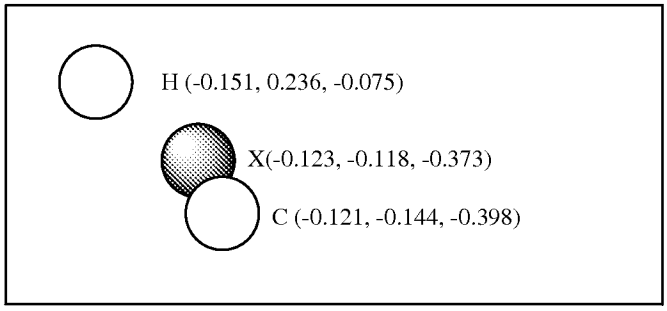
With reference to the claims, the "third process B3 of deleting said two atoms having the shortest interatomic distance…" produces a weighted average. Weighted average coordinates of the atoms" may be carried out as follows:



The upper left part is extracted from of the Figure 2 (C).

Generated pseudo-atom X was obtained as arithmetic mean when the two atoms were the same entities. However, if hetero atomic positions are predicted to be more important than those of hydrogen, atomic weights, for example, could be considered.

x=(-0.151*1.00-0.121*12.01)/(1.00+12.01)=-0.123
y=(0.236*1.00-0.144*12.01)/(1.00+12.01)=-0.118
z=(-0.075-0.398*12.01)/(1.00+12.01)=-0.373



With respect to process C, the interactions between respective atoms of said plural molecules is calculated. In the specification, Figure 3 illustrates that a spreadsheet table may be used to perform the partial least squares analysis.

In the case of the CoMFA, the interactions tabulated in the spreadsheet may be calculated by using Lenard-Jones potentials and electrostatic potentials and given as energy unit (Kcal/mol). On the other hand, all of the interactions used in the examples were dimensionless values. For example, the SEAL evaluation function gave similarity indices. The interaction values are not restricted to the energy term since, for example, the COMSIA used the SEAL evaluation would function as the same.

With respect to the statistical analysis step D, Cross-Validation (CV) is a reliable technique for testing the predictivity of models. With QSAR analysis in PLS methods, CV is a standard validation. Leave-One-Out Cross-Validation is one of the validation methods utilized with the PLS method. The predictive power of the models is assessed using cross validated coefficient (q2). The optimal number of PLS components, not a principal component, is usually chosen from the analysis with the highest q2 (cross-validated r2) value. In the specification, the components or “plural components” refer to the above PLS components when the PLS method is chosen as a statistical method.

Partial least squares regression (PLS-regression) is a statistical method that bears some relation to principal components regression. The equation:

Activity = y + a x S01 + b x S02 + … z x E50 …

may be obtained from the PLS calculation results. In the above equation:

"Activity" is the estimated or predicted biological activity such as binding affinity values and IC50 values. Usually –log(IC50) value would be used.

"y" is the value for regression coefficient for the intercept;

"a, b, …., z" are values for regression coefficient;

"S01, S02, ..., E50" are values for interactions between represented point and each molecules, for example, S01 value is steric interaction between one of the represented point and each molecules. E50 value is electrostatic interaction, for example.

Response to rejection 2A

The Examiner has objected to claim 1 as being directed to generating a QSAR relationship for a compound generated from a plurality of molecules. The Examiner maintains that the claim does not address how the compound is being generated.

Applicants respectfully request reconsideration in that the claim recites a computer-based method for generating a three-dimensional quantitative structure-activity relationship **of** a chemical compound. The claim does not purport to cover the actual fabrication of the chemical compound. Thus, the steps one would employ to manufacture the actual molecule are not encompassed by claim 1. Rather, the claimed method provides a structure-activity relationship, which can be expressed on a computer display, for example, to allow researchers to test different potential molecular forms for suitability for a desired biological activity. The technique is highly useful in that

it allows many thousands of molecular variations to be studied quickly, without the need to perform wet chemistry on each and every molecular variation.

Accordingly, applicants submit that claim 1 does particularly point out and distinctly claim the subject matter which applicants regard as the invention. Reconsideration is respectfully requested.

Response to rejection 2B

The Examiner has objected to the claims as reciting a related "pharmacological activity," when that term is not defined in the specification. Applicants have therefore amended the claims to recite "biological activity," which term is used in the specification. Support may be found at paragraphs [0001], [0002], [0008], and [0012]. Notably, at paragraph [0012], the Applicants cite J. Med. Chem. 1994, which demonstrates that "biological activity" has a well understood meaning in this art. Reconsideration in view of the amendment is therefore respectfully requested.

Response to rejection 2C

In this rejection, the Examiner has questioned how atoms may have "interaction" with "represented points." Applicants have attempted to address this issue in the above Overview of Applicants' Method. To reiterate, unlike with conventional techniques, the applicants' method does not care about the atom type being substituted. Thus, nominal values can be given to the represented point, e.g., charge = +1 and radius = 1 Angstrom. In the case of rapid molecular superposition evaluation function 2-A and indicator variables 2-D, interactions between the represented point and the atoms on

the molecules may simply be calculated by the distance and the chemical entities of the atoms on the molecules.

At first blush, it would seem that applicants' method is discarding important information (i.e., the atom type, and the associated electrostatic or hydrophobic properties associated therewith). However, the applicants have determined that they can achieve useful results by discarding this information and instead basing the analysis on the geometric position of the atoms—represented as "representative points."

Accordingly, while the applicants' method is admittedly different from standard QSAR techniques that would need to know the types of the atoms making up a molecule, applicants submit that their claims accurately reflect, and distinctly claim, their inventive method. Reconsideration is respectfully requested.

Response to rejection 2D

The Examiner has objected to Step C, which recites the calculating of interactions. The Examiner has noted that the clustering steps B1-B5 indeed will reduce the number of represented points as atoms are "deleted" in favor of a representative pseudo-atom point. As applicants have explained above, the interactions are calculated by treating all points the same (e.g., a charge of +1 and a radius of 1 Angstrom) and then using known interaction calculation techniques. While such interactions would not necessarily correlate to actual energy terms (as would be the case in interaction between actual atoms in a molecule), the interaction values still provide a *relative* measure that the applicants method is able to use. Accordingly, it is

respectfully submitted that the claims are accurate and particularly point out the inventive aspects of the applicants' method.

Response to rejection 2E

The Examiner has objected to claim 1, process D, which relates to correlating statistical analysis of interactions. This rejection is understood to be based on the difficulty the Examiner was having with how applicants' method operates upon "interaction" data among represented points. In view of the explanation given above, applicants submit that this basis for rejection has been adequately addressed. Reconsideration is respectfully requested.

Response to rejection 2F

The Examiner further objects to step D, which relates to "calculating correlation with pharmacological activity," where the term "pharmacological activity" was deemed vague. This was addressed by amendment as set forth in the remarks for rejection 2B above. Applicants therefore submit that the basis for this rejection has been rendered moot.

Response to rejection 2G

The Examiner has additionally objected to step D as reciting "forming an activity prediction formula." The Examiner states that "forming an activity prediction formula" is not taught in the specification.

Applicants would respectfully point out that the concept of an "activity prediction formula" is described in paragraphs [0009] and [0121] of applicants' specification. As explained in paragraph [0009], CoMFA fields are calculated for each one of the superposed molecules, and used as three-dimensional structure descriptors for each molecule to thereby statistically analyze the relationship with activity values. As explained, a partial least squares analysis can be used. Thus, the "activity prediction formula" can be seen as an expression of the *relationship* between three-dimensional structure descriptors and activity values.

It is therefore respectfully submitted that the terminology "activity predicting formula" is explained in the specification at paragraph [0009] and is thereafter used in context of applicants' method at paragraph [0121]. Reconsideration is respectfully requested.

Response to rejection 2H

The Examiner has further found unclear in step E how the activity value for each atom is overlayed on a region of one compound. As understood, the Examiner is pointing out that the claim appears to recite that an activity prediction value is assigned to the plurality of molecules—as a group. Applicants have therefore amended the claim to recite that the activity prediction value is assigned to each atom of at least one of the plurality of molecules. Thus, the claim no longer recites that a single activity prediction value is being overlayed on a plurality of different molecules, which would presumably have different amounts of atoms. Reconsideration in view of this amendment is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

Claims 1, 4, 7 and 8 also stand rejected under 35 U.S.C. § 112, first paragraph (written description), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention. Claims 1, 4, 7 and 8 further stand rejected under 35 U.S.C. § 112, first paragraph (enablement), as failing to comply with the enablement requirement.

Response to Rejection A

The Examiner asserts that new matter was introduced when the phrase "assigning activity prediction values to each atom" was added to the claims. Applicants have above addressed the fact that activity prediction formulas are defined in the specification at paragraphs [0009] and [0121]. In addition, reference is made to Figure 3, which shows a spreadsheet having an "Activity" column containing values (5.1, 6.8, …) which are calculated as illustrated in the formula appearing below the figure. From this formula, it is apparent that the individual atoms (S01, S02, …) each have assigned values from which the disclosed calculation is made. Accordingly, it is respectfully submitted that the claim language is supported by the specification and that no new matter has been added.

Response to Rejection B

As best understood, the basis of this rejection is the same as 2H above. Applicants have amended the claim as discussed above and thus believe that this rejection is now moot.

Response to Rejection B (second occurrence)

The Examiner objects here to Step D "forming an activity prediction formula." Applicants believe this issue has been addressed above in connection with issues 2G and Rejection A of this part. Reconsideration is therefore respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The basis of this rejection is applicants' teaching of the activity prediction formula. The Examiner has noted that applicants' Figure 3 contains a spreadsheet containing activity prediction values. Beneath that spreadsheet is an equation that explains that the overall activity prediction value is calculated from the activity prediction values of the individual points.

As explained in the applicants' specification, a Partial Least Squares (PLS) analysis is used in Step 5 to associate the activity prediction values with the individual points. See paragraph [0121]. Partial Least Squares is a well known technique whereby each compound is represented as a linear model comprising the concatenation of the various parameters associated with each atom (or represented point) within the compound. Thus, in Figure 3, Compound 1 would be represented as the linear model summing all the steric interactions (S01, S02, S03…), and all of the electrostatic

interactions (E01, E02, E03…). These individual interactions are determined, as explained above, based on the geometric relationships of the represented points. As explained previously, since these interactions assume all points they have the same charge and size. Thus, the values used are affected by geometric configuration, but not by the actual charge and size of the atoms the points replace.

Applicants submit that use of the PLS analysis would be well within the skill in the art and thus the specification provides an enabling disclosure to one of skill in this art.

REJECTION UNDER 35 U.S.C. § 101

Claims 1, 4, 7 and 8 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter. This rejection is respectfully traversed.

Applicants have amended the claims to include that the processing steps are performed by programmed computer. Support for this amendment may be found at page 6, paragraph [0014], of the published specification (2006/0080073 A1). Thus, as recited, the applicants' method is performed using a specific machine and thus the "machine" component of the machine-or-transformation (M-T) test is now met. In addition, because the data being analyzed by the applicants' method corresponds to real-world data (molecular parameters) that are transformed into a 3D visual representation, it is further submitted that the method meets the transformation branch of the M-T test. Reconsideration is respectfully requested.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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